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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/015,385 | 12/12/2001 | Kevin P. Baker | GNE.2830P1C51 | 9906 |

30313 7590 07/01/2004

KNOBBE, MARTENS, OLSON & BEAR, LLP
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FOURTEENTH FLOOR
IRVINE, CA 92614

| EXAMINER | |
|---|---|
| MCKELVEY, TERRY ALAN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1636 | |

DATE MAILED: 07/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/015,385 | BAKER ET AL. | |
| | Examiner | Art Unit | |
| | Terry A. McKelvey | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 28-47 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 28-47 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 12 December 2001 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 9/02.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

**DETAILED ACTION**

***Priority***

According to the priority statement of 9/9/02 (in related application 10/006,856), it appears that the claimed subject matter defined in the instant application is alleged by the applicant to be supported by the parent application no. 60/100,584, filed 9/16/98. However, based upon the information given by applicant and an inspection of the patent applications, the examiner has concluded that the subject matter defined in this application is supported by the disclosure in application no. PCT/US00/04342, filed 2/18/00 but is not supported by any of the other earlier filed applications because in the earlier applications, the claimed invention lacks specific and substantial utility and thus correspondingly lack enablement under 35 USC 112, first paragraph. Prior to the application filed 2/18/00, the earlier applications merely indicate that the protein encoded by the claimed nucleic acids have some degree of similarity to neuropsin, a serine protease. The only disclosed utilities for the nucleic acid is for encoding the protein, or non-specific and non-substantial general utilities such as use as a probe. There is no well-

established utility for these uses because the actual function of the protein encoded by the claimed nucleic acid is not known or disclosed by the earlier applications. The application-asserted utilities are not specific and substantial because some sequence similarity (about 50%) to a particular serine protease, neuropsin, as indicated in the rejection below, does not provide any information about the specific target of the new serine protease (assuming it is one) and thus one would not know what the specific utility of the protein (and thus the specific utility of the nucleic acid). It lacks a substantial utility because it would require carrying out further research to determine the specific target of the alleged serine protease so that a specific utility for the nucleic acid encoding the protein could be determined. Accordingly, because the applications filed before 2/18/00 fail to provide a specific and substantial utility for the claimed nucleic acids, the skilled artisan would not know how to use the nucleic acids which lack a specific and substantial utility. Thus, the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The subject matter defined in claims 28-47 have the effective filing date of 2/18/00.

Should the applicant disagree with the examiner's factual determination above, it is incumbent upon the applicant to provide the serial number and specific page number(s) of any parent application filed prior to 2/18/00 which specifically supports the particular claim limitation for each and every claim limitation in all pending claims which applicant considers to have been in possession of and fully enabled for prior to 2/10/00.

Also, applicants are requested to provide a similar concise claim of priority for the instant application that is supplied in the two PRO1303-related applications, 10/006,856 and 10/006,116.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-32, 39-40, and 44-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid having

100% nucleic acid sequence identity to a nucleic acid encoding the polypeptide of SEQ ID NO:194 or the mature form thereof (or drawn to a nucleic acid encoding a polypeptide having the function of affecting glucose or FFA uptake by primary rat adipocytes), does not reasonably provide enablement for an isolated nucleic acid not identical to a nucleic acid encoding at least the mature form of SEQ ID NO:194 or a nucleic acid which encodes a polypeptide which does not have this activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the quantity of experimentation necessary, the relative skill levels of those in the art, and the breadth of the claims.

The claims are drawn to a nucleic acid having at least 80% nucleic acid identity to a nucleic acid encoding a polypeptide of SEQ ID NO:194 or the extracellular domain thereof, both referred to as PRO1303. There is no functional limitation to the polypeptides encoded by the nucleic acid in the claims. Applicants have taught the polypeptide consisting of the extracellular domain or, more accurately, the mature form of SEQ ID NO:194, as well as the putative signal sequence. This polypeptide was shown to affect glucose or FFA uptake by primary rat adipocytes on the basis of an assay measuring this activity (Example 149, pages 511-512).

The claim encompasses an unreasonable number of inoperative nucleic acids because they encompass nucleic acids not encoding a polypeptide and nucleic acids encoding polypeptides having no functional limitation, which nucleic acids or proteins encoded by the nucleic acids the skilled artisan would not know how to use. While the specification suggests that the polypeptide of SEQ ID NO:194 is a serine protease related to neuropsin, the specific substrate specificity is undisclosed. Since PRO1303 is a secreted protein, it would be expected that the mature form would be sufficient for function in the absence of the secretory

signal. As opposed to the claims, what is disclosed about PRO1303 is narrow: nucleic acids encoding a single polypeptide with two disclosed functions and no other obvious specific functions. The skill in the serine protease art is not high because there are several different classes of serine proteases and even within classes, such as human kallikreins, which the instant polypeptide is a member of, each family member exhibits a high degree of substrate specificity (which is different for each family member) (Yousef et al, Anticancer Research, Vol. 19, pages 2843-2852 (1999), see page 2843, column 2). Therefore, knowledge of one serine protease's structure and function does not provide predictability about function of a structurally related serine protease, even within the same class.

There are no working examples of nucleic acids that are less than 100% identical to the nucleic acids that encode the polypeptide of SEQ ID NO:194 or the mature form thereof. The skilled artisan would not know how to use non-identical nucleic acids or the encoded non-identical polypeptides on the basis of teachings in the prior art or the specification unless they encode polypeptides that possess the glucose or FFA uptake function disclosed in the

instant specification. While the specification generally describes properties of serine proteases, it is acknowledged by the cited art that serine proteases such as kallikreins are diverse in function and structure. The specification does not provide guidance for using nucleic acids related to (i.e., 80%-99% identity) but not identical to nucleic acids encoding a polypeptide of SEQ ID NO:194 which do not encode a polypeptide that has the disclosed activity shown for PRO1303. The claims are broad because they do not require the polypeptide encoded by the claimed nucleic acid to be identical to the disclosed sequence and because the claims have no functional limitation.

For these reasons, which include the complexity and unpredictability of the nature of the invention and art in terms of the diversity of serine proteases and lack of knowledge about function9s) of encompassed polypeptides structurally related to SEQ ID NO:194, the one limited working example of nucleic acid encoding PRO1303 polypeptide which has its one demonstrated function, affecting glucose or FFA uptake by adipocytes, the lack of direction or guidance for using nucleic acids that encode polypeptides that are not identical to at least the extracellular domain of SEQ ID NO:194, and the breadth of

the claims for structure without function, it would require undue experimentation to use the invention commensurate in scope with the claims.

Claims 28-32, 39-40, and 44-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a nucleic acid having at least 80%, 85%, 90%, 95%, or 99% nucleic acid sequence identity to a nucleic acid encoding a polypeptide of SEQ ID NO:194 or the extracellular domain thereof, both referred to as PRO1303. The claims do not require that the nucleic acid encode a polypeptide that possesses any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of nucleic acids that is defined only by sequence identity.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In the instant case, the only factor present in the claims is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented

what is now is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or identification. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated nucleic acids encoding polypeptides comprising the amino acid sequence set forth in SEQ ID NO:194, but not the full breadth of the claims meets the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C.

112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The protein identified as PRO1303 is a soluble protein, and is not disclosed as being expressed on a cell surface. Accordingly, the limitation that the claimed polypeptide comprises an "extracellular domain" (for example, see claim 23 (c) and (d)) is indefinite, as the art does not recognize soluble proteins as having such domains. Further, if the polypeptide had an extracellular domain, the recitation of "the extracellular domain" ... "lacking its associated signal sequence" (claim 23 (d), for example) is indefinite because a signal sequence is not generally considered to be part of an extracellular domain, since signal sequences are cleaved from said domains in the process of secretion from the cell.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 28-37, 41-44, and 46 are rejected under 35 U.S.C. 102(a) as being anticipated by Yousef et al.

Yousef et al teach an isolated nucleic acid which is a genomic clone (Reversed contig 37, Figure 1; Table VI) which encodes KLK-L5, which has 100% identity to SEQ ID NO:194 (although Yousef et al only identify some of the exons encoded by the genomic DNA which are a part of KLK-L5). Even though the precise polypeptide sequence and isolated complete protein is not taught by the reference, the genomic nucleic acid encoding the protein is taught and would be expected to have 100% nucleic acid identity to a

nucleic acid encoding SEQ ID NO:194, SEQ ID NO:194 without the signal peptide, and the "extracellular domain" of SEQ ID NO:194. See the attached sequence comparison. Vectors comprising the isolated nucleic acid and host cells comprising the vector, are also taught (Figure 1).

Claims 41-47 are rejected under 35 U.S.C. 102(e) as being anticipated by Ni et al (U.S. Patent No. 6,566,498 B1).

Ni et al (at Figure 3; columns 22-23) teach an isolated nucleic acid which has a high degree of identity to SEQ ID NO:193 (97.9%) over a large part of the sequence (about 500 base pairs). See the attached sequence comparison. This large region of near identity is more than sufficient in length to support hybridization with SEQ ID NO:193 under stringent conditions. Vectors comprising the isolated nucleic acid and host cells comprising the vector, wherein the nucleic acid is operably linked to control sequences recognized by a host cell transformed with the vector, such as E. coli or yeast cells, are also taught (columns 22-23).

***Conclusion***

No claims are allowed.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is 703-872-9306. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should be directed to Terry A. McKelvey whose telephone number is (571) 272-0775. The examiner can normally be reached on Monday through Friday, except for Wednesdays, from about 7:30 AM to about 6:00 PM. A phone message left at this number will be responded to as soon as

possible (i.e., shortly after the examiner returns to his office).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached at (571) 272-0781.

**Terry A. McKelvey, Ph.D.**
**Primary Examiner**
**Art Unit 1636**

June 27, 2004

Attachments to the Detailed Action

GenCore version 5.1.6


OM protein - protein search, using sw model

Run on: June 16, 2004, 20:26:41 ; Search time 18 Seconds
(without alignments)
717.411 Million cell updates/sec

Title: US-10-015-385A-194
Perfect score: 1374
Sequence: 1 MGLSIFLLLCVLGLSQAATP.....GVYTYICKYVDWIRMIMRNN 248

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 141681 seqs, 52070155 residues

Total number of hits satisfying chosen parameters: 141681

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Database : SwissProt_42:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

| Result No. | Score | % Query Match | Length | DB | ID | Description |
|---|---|---|---|---|---|---|
| 1 | 1374 | 100.0 | 248 | 1 | KLKC_HUMAN | Q9ukr0 homo sapien |
| 2 | 630.5 | 45.9 | 260 | 1 | KLK8_HUMAN | O60259 homo sapien |
| 3 | 622.5 | 45.3 | 260 | 1 | NRPN_MOUSE | Q61955 mus musculu |
| 4 | 621.5 | 45.2 | 260 | 1 | NRPN_RAT | O88780 rattus norv |
| 5 | 618.5 | 45.0 | 250 | 1 | KLKB_HUMAN | Q9ubx7 homo sapien |
| 6 | 599 | 43.6 | 256 | 1 | KLKF_HUMAN | Q9h2r5 homo sapien |
| 7 | 569.5 | 41.4 | 248 | 1 | TRY3_CHICK | Q90629 gallus gall |
| 8 | 569.5 | 41.4 | 251 | 1 | KLKE_HUMAN | Q9p0g3 homo sapien |
| 9 | 568.5 | 41.4 | 250 | 1 | KLK9_HUMAN | Q9ukq9 homo sapien |
| 10 | 567 | 41.3 | 277 | 1 | KLKD_HUMAN | Q9ukr3 homo sapien |
| 11 | 566 | 41.2 | 248 | 1 | TRY2_CHICK | Q90628 gallus gall |
| 12 | 565 | 41.1 | 248 | 1 | TRY1_CHICK | Q90627 gallus gall |
| 13 | 564.5 | 41.1 | 293 | 1 | KLK5_HUMAN | Q9y337 homo sapien |
| 14 | 564 | 41.0 | 276 | 1 | KLKA_HUMAN | O43240 homo sapien |
| 15 | 563 | 41.0 | 244 | 1 | TRY2_XENLA | P70059 xenopus lae |
| 16 | 561 | 40.8 | 231 | 1 | TRYP_PIG | P00761 sus scrofa |
| 17 | 561 | 40.8 | 243 | 1 | TRY1_BOVIN | P00760 bos taurus |
| 18 | 561 | 40.8 | 244 | 1 | KLK6_HUMAN | Q92876 homo sapien |
| 19 | 555 | 40.4 | 243 | 1 | TRY1_XENLA | P19799 xenopus lae |
| 20 | 555 | 40.4 | 253 | 1 | KLK7_HUMAN | P49862 homo sapien |
| 21 | 553 | 40.2 | 246 | 1 | TRY2_MOUSE | P07146 mus musculu |
| 22 | 550 | 40.0 | 247 | 1 | TRY2_BOVIN | Q29463 bos taurus |
| 23 | 546 | 39.7 | 247 | 1 | TRY2_CANFA | P06872 canis famil |
| 24 | 545 | 39.7 | 246 | 1 | TRY1_CANFA | P06871 canis famil |
| 25 | 544.5 | 39.6 | 247 | 1 | TRY3_RAT | P08426 rattus norv |
| 26 | 543 | 39.5 | 246 | 1 | TRY1_RAT | P00762 rattus norv |
| 27 | 540 | 39.3 | 238 | 1 | TRY3_SALSA | P35033 salmo salar |
| 28 | 533.5 | 38.8 | 247 | 1 | TRY4_RAT | P12788 rattus norv |
| 29 | 533 | 38.8 | 246 | 1 | TRY2_RAT | P00763 rattus norv |
| 30 | 527.5 | 38.4 | 261 | 1 | KLK7_RAT | P36373 rattus norv |
| 31 | 521.5 | 38.0 | 246 | 1 | KLK_PIG | P00752 sus scrofa |
| 32 | 521.5 | 38.0 | 261 | 1 | KLK6_MOUSE | P15947 mus musculu |
| 33 | 519 | 37.8 | 246 | 1 | TRYA_RAT | P32821 rattus norv |
| 34 | 518 | 37.7 | 246 | 1 | TRYB_RAT | P32822 rattus norv |
| 35 | 518 | 37.7 | 261 | 1 | KLK8_RAT | P36374 rattus norv |
| 36 | 513.5 | 37.4 | 231 | 1 | TRY2_SALSA | P35032 salmo salar |
| 37 | 513.5 | 37.4 | 239 | 1 | KLK2_CAVPO | P12323 cavia porce |
| 38 | 510.5 | 37.2 | 261 | 1 | KLK3_MOUSE | P00756 mus musculu |
| 39 | 508 | 37.0 | 242 | 1 | TRY1_SALSA | P35031 salmo salar |
| 40 | 505 | 36.8 | 260 | 1 | ESTA_CANFA | P09582 canis famil |
| 41 | 503 | 36.6 | 263 | 1 | KLKR_PRANA | P32824 praomys nat |
| 42 | 502 | 36.5 | 259 | 1 | KLKC_RAT | P36376 rattus norv |
| 43 | 501 | 36.5 | 247 | 1 | TRY2_HUMAN | P07478 homo sapien |
| 44 | 499.5 | 36.4 | 241 | 1 | TRYX_GADMO | Q91041 gadus morhu |
| 45 | 498 | 36.2 | 254 | 1 | KLK4_HUMAN | Q9y5k2 homo sapien |

ALIGNMENTS

RESULT 1
KLKC_HUMAN
ID KLKC_HUMAN STANDARD; PRT; 248 AA.
AC Q9UKR0; Q9UKR1;
DT 16-OCT-2001 (Rel. 40, Created)
DT 16-OCT-2001 (Rel. 40, Last sequence update)
DT 16-OCT-2001 (Rel. 40, Last annotation update)
DE Kallikrein 12 precursor (EC 3.4.21.-) (Kallikrein-like protein 5)
DE (KLK-L5).
GN KLK12 OR KLKL5.
OS Homo sapiens (Human).
OC Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
OX NCBI_TaxID=9606;
RN [1]
RP SEQUENCE FROM N.A. (ISOFORM 1).
RX MEDLINE=20118156; PubMed=10652563;
RA Yousef G.M., Luo L.-Y., Diamandis E.P.;
RT "Identification of novel human kallikrein-like genes on chromosome
RT 19q13.3-q13.4.";
RL Anticancer Res. 19:2843-2852(1999).
RN [2]
RP SEQUENCE FROM N.A. (ISOFORMS 1 AND 2).
RA Yousef G.M., Magklara A., Scorilas A., Diamandis E.P.;
RT "Cloning of new alternatively spliced forms of the kallikrein-like
RT gene 5 (KLK-L5).";
RL Submitted (NOV-1999) to the EMBL/GenBank/DDBJ databases.
RN [3]
RP SEQUENCE FROM N.A. (ISOFORM 1).
RX MEDLINE=20510030; PubMed=11054574;
RA Gan L., Lee I., Smith R., Argonza-Barrett R., Lei H., McCuaig J.,
RA Moss P., Paeper B., Wang K.;
RT "Sequencing and expression analysis of the serine protease gene
RT cluster located in chromosome 19q13 region.";
RL Gene 257:119-130(2000).
RN [4]
RP SEQUENCE FROM N.A. (ISOFORM 2).
RA Lamerdin J.E., McCready P.M., Skowronski E., Viswanathan V.,
RA Burkhart-Schultz K., Gordon L., Dias J., Ramirez M., Stilwagen S.,
RA Phan H., Velasco N., Do L., Regala W., Terry A., Brower A., Garnes J.,
RA Danganan L., Erler A., Christensen M., Georgescu A., Avila J., Liu S.,
RA Andreise T., Trankheim M., Attix C., Amico-Keller G., Coefield J.,
RA Duarte S., Lucas S., Bruce R., Thomas P., Quan G., Kronmiller B.,
RA Arellano A., Sanders C., Ow D., Nolan M., Trong S., Kobayashi A.,
RA Olsen A.S., Carrano A.V.;
RT "Sequence analysis of chromosome 19q13.4.";
RL Submitted (OCT-2000) to the EMBL/GenBank/DDBJ databases.
CC -!- SUBCELLULAR LOCATION: Secreted (Probable).
CC -!- ALTERNATIVE PRODUCTS:
CC Event=Alternative splicing; Named isoforms=2;
CC Name=1;
CC IsoId=Q9UKR0-1; Sequence=Displayed;
CC Name=2;
CC IsoId=Q9UKR0-2; Sequence=VSP_005403;
CC -!- SIMILARITY: Belongs to peptidase family S1. Kallikrein subfamily.
CC ---

```
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CC   ---------------------------------------------------------------------------
DR   EMBL; AF135025; AAD26426.2; -.
DR   EMBL; AF135025; AAF06065.1; -.
DR   EMBL; AF243527; AAG33365.1; -.
DR   EMBL; AC011473; AAG23258.1; -.
DR   HSSP; P00763; 1DPO.
DR   MEROPS; S01.020; -.
DR   Genew; HGNC:6360; KLK12.
DR   MIM; 605539; -.
DR   GO; GO:0005576; C:extracellular; NAS.
DR   GO; GO:0004252; F:serine-type endopeptidase activity; NAS.
DR   GO; GO:0006508; P:proteolysis and peptidolysis; NAS.
DR   InterPro; IPR009003; Cys_Ser_trypsin.
DR   InterPro; IPR001254; Peptidase_S1.
DR   InterPro; IPR001314; Peptidase_S1A.
DR   Pfam; PF00089; trypsin; 1.
DR   PRINTS; PR00722; CHYMOTRYPSIN.
DR   SMART; SM00020; Tryp_SPc; 1.
DR   PROSITE; PS50240; TRYPSIN_DOM; 1.
DR   PROSITE; PS00134; TRYPSIN_HIS; 1.
DR   PROSITE; PS00135; TRYPSIN_SER; 1.
KW   Hydrolase; Serine protease; Glycoprotein; Signal;
KW   Alternative splicing.
FT   SIGNAL        1     17       POTENTIAL.
FT   CHAIN        18    248       KALLIKREIN 12.
FT   ACT_SITE     62     62       CHARGE RELAY SYSTEM (BY SIMILARITY).
FT   ACT_SITE    108    108       CHARGE RELAY SYSTEM (BY SIMILARITY).
FT   ACT_SITE    200    200       CHARGE RELAY SYSTEM (BY SIMILARITY).
FT   DISULFID     28    161       BY SIMILARITY.
FT   DISULFID     47     63       BY SIMILARITY.
FT   DISULFID    133    235       BY SIMILARITY.
FT   DISULFID    140    206       BY SIMILARITY.
FT   DISULFID    172    186       BY SIMILARITY.
FT   DISULFID    196    222       BY SIMILARITY.
FT   CARBOHYD     24     24       N-LINKED (GLCNAC. . .) (POTENTIAL).
FT   CARBOHYD    163    163       N-LINKED (GLCNAC. . .) (POTENTIAL).
FT   VARSPLIC    236    248       KYVDWIRMIMRNN -> NSTLVGLGTSWNFNSCQPF (in
FT                                isoform 2).
FT                                /FTId=VSP_005403.
SQ   SEQUENCE   248 AA;  26733 MW;  BB473E98F8BAF703 CRC64;

  Query Match             100.0%;  Score 1374;  DB 1;  Length 248;
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  Matches  248;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 MGLSIFLLLCVLGLSQAATPKIFNGTECGRNSQPWQVGLFEGTSLRCGGVLIDHRWVLTA 60
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Db          1 MGLSIFLLLCVLGLSQAATPKIFNGTECGRNSQPWQVGLFEGTSLRCGGVLIDHRWVLTA 60

Qy         61 AHCSGSRYWVRLGEHSLSQLDWTEQIRHSGFSVTHPGYLGASTSHEHDLRLLRLRLPVRV 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 AHCSGSRYWVRLGEHSLSQLDWTEQIRHSGFSVTHPGYLGASTSHEHDLRLLRLRLPVRV 120

Qy        121 TSSVQPLPLPNDCATAGTECHVSGWGITNHPRNPFPDLLQCLNLSIVSHATCHGVYPGRI 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 TSSVQPLPLPNDCATAGTECHVSGWGITNHPRNPFPDLLQCLNLSIVSHATCHGVYPGRI 180

Qy        181 TSNMVCAGGVPGQDACQGDSGGPLVCGGVLQGLVSWGSVGPCGQDGIPGVYTYICKYVDW 240
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Db        181 TSNMVCAGGVPGQDACQGDSGGPLVCGGVLQGLVSWGSVGPCGQDGIPGVYTYICKYVDW 240

Qy        241 IRMIMRNN 248
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Db        241 IRMIMRNN 248
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RESULT 2
KLK8_HUMAN
ID   KLK8_HUMAN     STANDARD;      PRT;   260 AA.
AC   O60259; Q9HCB3; Q9UIL9; Q9UQ47;
DT   15-JUL-1999 (Rel. 38, Created)
DT   15-JUL-1999 (Rel. 38, Last sequence update)
DT   15-MAR-2004 (Rel. 43, Last annotation update)
DE   Neuropsin precursor (EC 3.4.21.-) (NP) (Kallikrein 8) (Ovasin) (Serine
DE   protease TADG-14) (Tumor-associated differentially expressed gene-14
DE   protein).
GN   KLK8 OR PRSS19 OR TADG14 OR NRPN.
OS   Homo sapiens (Human).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
OX   NCBI_TaxID=9606;
RN   [1]
RP   SEQUENCE FROM N.A. (ISOFORM 1).
RC   TISSUE=Hippocampus;
RX   MEDLINE=98372070; PubMed=9714609;
RA   Yoshida S., Taniguchi M., Hirata A., Shiosaka S.;
RT   "Sequence analysis and expression of human neuropsin cDNA and gene.";
RL   Gene 213:9-16(1998).
RN   [2]
RP   SEQUENCE FROM N.A. (ISOFORMS 1 AND 2).
RC   TISSUE=Brain;
RX   MEDLINE=99203457; PubMed=10102990;
RA   Mitsui S., Tsuruoka N., Yamashiro K., Nakazato H., Yamaguchi N.;
RT   "A novel form of human neuropsin, a brain-related serine protease, is
RT   generated by alternative splicing and is expressed preferentially in
RT   human adult brain.";
RL   Eur. J. Biochem. 260:627-634(1999).
RN   [3]
RP   SEQUENCE FROM N.A. (ISOFORM 1).
RC   TISSUE=Ovary;
RX   MEDLINE=99413504; PubMed=10485494;
RA   Underwood L.J., Tanimoto H., Wang Y., Shigemasa K., Parmley T.H.,
RA   O'Brien T.J.;
RT   "Cloning of tumor-associated differentially expressed gene-14, a novel
RT   serine protease overexpressed by ovarian carcinoma.";
RL   Cancer Res. 59:4435-4439(1999).
RN   [4]
RP   SEQUENCE FROM N.A. (ISOFORM 1).
RA   Gan L., Gelinas R., Gown A.M., Moss P., Smith R., Wang K.;
RT   "Molecular cloning and characterization of a novel serine protease,
RT   ovasin, a potential molecular marker for ovarian carcinomas.";
RL   Submitted (SEP-1998) to the EMBL/GenBank/DDBJ databases.
RN   [5]
RP   SEQUENCE FROM N.A. (ISOFORM 1).
RX   MEDLINE=20510030; PubMed=11054574;
RA   Gan L., Lee I., Smith R., Argonza-Barrett R., Lei H., McCuaig J.,
RA   Moss P., Paeper B., Wang K.;
RT   "Sequencing and expression analysis of the serine protease gene
RT   cluster located in chromosome 19q13 region.";
RL   Gene 257:119-130(2000).
RN   [6]
RP   SEQUENCE OF 1-164 FROM N.A. (ISOFORM 1).
RA   Lamerdin J.E., McCready P.M., Skowronski E., Viswanathan V.,
RA   Burkhart-Schultz K., Gordon L., Dias J., Ramirez M., Stilwagen S.,
RA   Phan H., Velasco N., Do L., Regala W., Terry A., Brower A., Garnes J.,
RA   Danganan L., Erler A., Christensen M., Georgescu A., Avila J., Liu S.,
RA   Andreise T., Trankheim M., Attix C., Amico-Keller G., Coefield J.,
RA   Duarte S., Lucas S., Bruce R., Thomas P., Quan G., Kronmiller B.,
RA   Arellano A., Sanders C., Ow D., Nolan M., Trong S., Kobayashi A.,
RA   Olsen A.S., Carrano A.V.;
RT   "Sequence analysis of chromosome 19q13.4.";
RL   Submitted (OCT-2000) to the EMBL/GenBank/DDBJ databases.
CC   -!- FUNCTION: Suggested to be involved in kindling epileptogenesis and
CC       hippocampal plasticity.
CC   -!- CATALYTIC ACTIVITY: Preferential cleavage: Arg-, Lys-.
CC   -!- SUBCELLULAR LOCATION: Secreted.
CC   -!- ALTERNATIVE PRODUCTS:
CC       Event=Alternative splicing; Named isoforms=2;
CC       Name=1;
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Qy        878 CCACCTCCACCCCCACCCCTTAACTTGGGTACCCCTCTGGCCCTCAGAGCACCAATATCT 937
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Db        526 CCACCTCCACCCCCACCCCTTAACTTGGGTACCCCTCTGGCCCTCAGAGCACCAATATCT 585

Qy        938 CCTCCATCACTTCCCCTAGCTCCACTCTTGTTGGCCTGGGAACTTCTTGGAACTTTAACT 997
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Db        586 CCTCCATCACTTCCCCTAGCTCCACTCTTGTTGGCCTGGGAACTTCTTGGAACTTTAACT 645

Qy        998 CCTGCCAGCCCTTCTAAGACCCACGAGCGGGGTGAGAGAAGTGTGCAATAGTCTGGAATA 1057
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Qy       1058 AATATAAATGAAGGAGGGGCAAAAAAAAAAAAAA 1091
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Db        706 AATATAAATGAAGGAGGGAAAAAAAAAAAAAAA 739


RESULT 4
AR337568
LOCUS       AR337568                840 bp    DNA     linear   PAT 17-AUG-2003
DEFINITION  Sequence 5 from patent US 6566498.
ACCESSION   AR337568
VERSION     AR337568.1  GI:33723963
KEYWORDS    .
SOURCE      Unknown.
  ORGANISM  Unknown.
            Unclassified.
REFERENCE   1  (bases 1 to 840)
  AUTHORS   Ni,J. and Ruben,S.M.
  TITLE     Human serine protease and serpin polypeptides
  JOURNAL   Patent: US 6566498-A 5 20-MAY-2003;
FEATURES             Location/Qualifiers
     source          1. .840
                     /organism="unknown"
                     /mol_type="genomic DNA"
ORIGIN

  Query Match             46.4%;  Score 506.4;  DB 6;  Length 840;
  Best Local Similarity   97.9%;  Pred. No. 1.1e-104;
  Matches  513;  Conservative    0;  Mismatches   11;  Indels    0;  Gaps    0;

Qy        568 CACCCACGGAACCCATTCCCGGATCTGCTCCAGTGCCTCAACCTCTCCATCGTCTCCCAT 627
              || |  | || ||  | ||||||||||||||||||||||||||||||||||||||||||||
Db        304 CAGCGGCAGACCCATTCCCCGGATCTGCTCCAGTGCCTCAACCTCTCCATCGTCTCCCAT 363

Qy        628 GCCACCTGCCATGGTGTGTATCCCGGGAGAATCACGAGCAACATGGTGTGTGCAGGCGGC 687
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Db        364 GCCACCTGCCATGGTGTGTATCCCGGGAGAATCACGAGCAACATGGTGTGTGCAGGCGGC 423

Qy        688 GTCCCGGGGCAGGATGCCTGCCAGGGTGATTCTGGGGGCCCCCTGGTGTGTGGGGGAGTC 747
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Db        424 GTCCCGGGGCAAGATGCCTGCCAGGGTGATTCTGGGGGCCCCCTGGTGTGTGGGGGAGTC 483

Qy        748 CTTCAAGGTCTGGTGTCCTGGGGGTCTGTGGGGCCCTGTGGACAAGATGGCATCCCTGGA 807
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Db        484 CTTCAAGGTCTGGTGTCCTGGGGGTCTGTGGGGCCCTGTGGACAAGATGGCATCCCTGGA 543

Qy        808 GTCTACACCTATATTTGCAAGTATGTGGACTGGATCCGGATGATCATGAGGAACAACTGA 867
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Qy        868 CCTGTTTCCTCCACCTCCACCCCCACCCCTTAACTTGGGTACCCCTCTGGCCCTCAGAGC 927
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Db        604 CCTGTTTCCTCCACCTCCACCCCCACCCCTTAACTTGGGTACCCCTCTGGCCCTCAGAGC 663

Qy        928 ACCAATATCTCCTCCATCACTTCCCCTAGCTCCACTCTTGTTGGCCTGGGAACTTCTTGG 987
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Db        664 ACCAATATCTCCTCCATCACTTCCCCTAGCTCCACTCTTGTTGGCCTGGGAACTTCTTGG 723

Qy        988 AACTTTAACTCCTGCCAGCCCTTCTAAGACCCACGAGCGGGGTGAGAGAAGTGTGCAATA 1047
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Db        784 GTCTGGAATAAATATAAATGAAGGAGGGAAAAAAAAAAAAAAA 827


RESULT 5
BD130047
LOCUS       BD130047                840 bp    DNA     linear   PAT 18-SEP-2002
DEFINITION  Human serine protease and serpin polypeptide.
ACCESSION   BD130047
VERSION     BD130047.1  GI:23224992
KEYWORDS    JP 2002502600-A/3.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 840)
  AUTHORS   Ruben,S.M. and Ni,J.
  TITLE     Human serine protease and serpin polypeptide
  JOURNAL   Patent: JP 2002502600-A 3 29-JAN-2002;
            HUMAN GENOME SCIENCES INC
COMMENT     OS   Homo sapiens (human)
            PN   JP 2002502600-A/3
            PD   29-JAN-2002
            PF   04-FEB-1999 JP 2000530597
            PR   06-FEB-1998 US    60/073961
            PI   STEVEN M RUBEN,JIAN NI
            PC
            C12N9/64,A61K38/48,A61P7/02,A61P7/04,A61P7/06,A61P29/00,A61P31/ PC
             00,
            PC   A61P35/00,A61P37/06,C07K14/81,C07K16/40,C12N1/15,C12N1/19, PC
             C12N1/21,
            PC   C12N5/10,C12N15/09,C12Q1/37,A61K37/547,C12N5/00,C12N15/00 CC
            Human serine protease and serpin polypeptide
            FH   Key             Location/Qualifiers
            FT   CDS             (115). .(603).
FEATURES             Location/Qualifiers
     source          1. .840
                     /organism="Homo sapiens"
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                     /db_xref="taxon:9606"
ORIGIN

  Query Match             46.4%;  Score 506.4;  DB 6;  Length 840;
  Best Local Similarity   97.9%;  Pred. No. 1.1e-104;
  Matches  513;  Conservative    0;  Mismatches   11;  Indels    0;  Gaps    0;

Qy        568 CACCCACGGAACCCATTCCCGGATCTGCTCCAGTGCCTCAACCTCTCCATCGTCTCCCAT 627
              || |  | || ||  | ||||||||||||||||||||||||||||||||||||||||||||
Db        304 CAGCGGCAGACCCATTCCCCGGATCTGCTCCAGTGCCTCAACCTCTCCATCGTCTCCCAT 363

Qy        628 GCCACCTGCCATGGTGTGTATCCCGGGAGAATCACGAGCAACATGGTGTGTGCAGGCGGC 687
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Db        364 GCCACCTGCCATGGTGTGTATCCCGGGAGAATCACGAGCAACATGGTGTGTGCAGGCGGC 423

Qy        688 GTCCCGGGGCAGGATGCCTGCCAGGGTGATTCTGGGGGCCCCCTGGTGTGTGGGGGAGTC 747
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Db        424 GTCCCGGGGCAAGATGCCTGCCAGGGTGATTCTGGGGGCCCCCTGGTGTGTGGGGGAGTC 483

Qy        748 CTTCAAGGTCTGGTGTCCTGGGGGTCTGTGGGGCCCTGTGGACAAGATGGCATCCCTGGA 807
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Qy        868 CCTGTTTCCTCCACCTCCACCCCCACCCCTTAACTTGGGTACCCCTCTGGCCCTCAGAGC 927
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Qy        928 ACCAATATCTCCTCCATCACTTCCCCTAGCTCCACTCTTGTTGGCCTGGGAACTTCTTGG 987
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